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[HLA-G: a tolerance molecule implicated in the escape of tumors from immunosurveillance].
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Heterogeneity of HLA-G gene transcription and protein expression in malignant melanoma biopsies.
Cancer Res. 1999 Apr 15;59(8):1954-60.
PMID: 10213506

1: *Proc Natl Acad Sci U S A* 1998 Apr 14;95(8):4510-5

HLA-G expression in melanoma: a way for tumor cells to escape from immunosurveillance.

Paul P, Rouas-Freiss N, Khalil-Daher I, Moreau P, Riteau B, Le Gal FA, Avril MF, Dausset J, Guillet JG, Carosella ED

Direction des Sciences du Vivant-Department de Recherche Medicale, Service de Recherches en Hemato-Immunologie, Commissariat a l'Energie Atomique, Hopital Saint-Louis, Centre Hayem, 1, Avenue Claude-Vellefaux, 75010 Paris, France.

Considering the well established role of nonclassical HLA-G class I molecules in inhibiting natural killer (NK) cell function, the consequence of abnormal HLA-G expression in malignant cells should be the escape of tumors from immunosurveillance. To examine this hypothesis, we analyzed HLA-G expression and NK sensitivity in human malignant melanoma cells. Our analysis of three melanoma cell lines and ex vivo biopsy demonstrated that (i) IGR and M74 human melanoma cell lines exhibit a high level of HLA-G transcription with differential HLA-G isoform transcription and protein expression patterns, (ii) a higher level of HLA-G transcription ex vivo is detected in a skin melanoma metastasis biopsy compared with a healthy skin fragment from the same individual, and (iii) HLA-G protein isoforms other than membrane-bound HLA-G1 protect IGR from NK lysis. It thus appears of critical importance to consider the specific role of HLA-G expression in tumors in the design of future cancer immunotherapies.

PMID: 9539768

HLA-G gene transcriptional regulation in trophoblasts and blood cells: differential binding of nuclear factors to a regulatory element located 1.1 kb from exon 1.

Moreau P, Paul P, Gourand L, Prost S, Dausset J, Carosella E, Kirszenbaum M

Department of Recherche Medicale, Hopital St-louis, Paris, France.

The HLA-G antigen is specifically expressed on trophoblasts at the maternal-fetal interface, while expression of classical class I HLA-A, -B, -C products is repressed in this tissue. The transcriptional level of the HLA-G gene is high in trophoblast cells and in JEG-3 choriocarcinoma cells, is markedly reduced in blood cells, and is shown here to be undetectable in the YT2C2 NK cell line. In an attempt to understand molecular mechanisms controlling cell-specific transcriptional regulation of the HLA-G gene in these cells, we focused our study on protein interaction with a 244-bp region located over 1.1 kb from exon 1, which has been shown to direct HLA-G expression in transgenic mouse trophoblast. Three specific complexes were detected, two of which are found exclusively in cells showing HLA-G transcriptional activity. The YT2C2 nuclear extracts contain restricted DNA-binding activity of an additional factor which could correlate with repression of HLA-G transcription in these cells.

PMID: 9021408

1: *Isr J Med Sci* 1996 Dec;32(12):1238-43 Related Articles, Books, LinkOut

HLA class I antigen expression in human solid tumors.

Klein B, Levin I, Klein T

Oncology Unit, Rabin Medical Center, Petah Tikva, Israel.

The expression of HLA class I antigens was studied by immunohistochemistry in various tumors in correlation with clinicopathologic characteristics. Reduced expression was observed in germ cell testicular cancer, kidney, prostate, gastric and colon cancer, and was associated with tumor aggressiveness, grade and penetration of the tumor through the organ wall. In bladder cancer reduced expression was associated with poor survival. Irradiation of brain tumors resulted in an increase in class I expression. Soluble class I levels were studied in breast and colon cancer patients and were found to be high in those with metastatic disease. The clinical relevance of reduced class I levels are discussed.

Publication Types:
- Review
- Review, tutorial

PMID: 9007163

1: *Semin Cancer Biol* 1999 Feb;9(1):55-9 Related Articles, Books, LinkOut

IDEAL

The regulation of HLA class I expression: is HLA-G the odd one out?

Gobin SJ, van den Elsen PJ

Department of Immunohematology and Blood Bank, Leiden University Medical Center, Albinusdreef 2, Leiden, 2333 ZA, The Netherlands.

The expression of HLA-G in extravillous cytotrophoblast cells coincides with a general lack of classical MHC class I expression in this tissue. This differential expression of HLA-G and classical HLA class I molecules in trophoblasts suggests a tight transcriptional control. Transactivation of classical MHC class I genes is mediated by two groups of juxtaposed cis -acting elements which can be viewed as regulatory modules. The most up-stream module consists of the enhancer A and ISRE, and mediates the constitutive and cytokine-induced expression. The recently identified S-X-Y module is important in the constitutive and CIITA mediated transactivation. Both modules are divergent in HLA-G rendering this gene unresponsive to NF-kappaB, IRF-1, and CIITA mediated induction pathways. However, other known regulatory sequences that could contribute to the tissue-specific expression of HLA-G have so far not been identified in the proximal promoter region (-1500 bp) and in the first five intronic sequences. This implies a unique regulation of HLA-G transcription. Here, the transcriptional control of HLA-G and classical class I molecules in trophoblast cells are discussed.

Publication Types:
- Review
- Review, tutorial

PMID: 10092551

1: *Tissue Antigens* 1996 Nov;48(5):609-14 Related Articles, Books, LinkOut

HLA-G transcription studies during the different stages of normal and malignant hematopoiesis.

Amiot L, Onno M, Renard I, Drenou B, Guillaudeux T, Le Bouteiller P, Fauchet R

Laboratoire d' Hematologie et de la biologie des cellules sanguines, Universite de Rennes I, France.

Specific expression of the non classical class I HLA-G gene on trophoblasts, the only fetal tissue in contact with maternal cells which lack MHC class I antigens, may indicate a role of this gene in fetal-maternal tolerance. We recently reported HLA-G transcription in peripheral blood leukocytes. In this work, we have investigated HLA-G transcription in hematopoietic stem cells, in different hematopoietic lineages and in malignant cells by using a RT-PCR technique. PCR amplification with primers specific to the exon 2 and the 3' untranslated region has enabled to detect HLA-G transcription in B and T cell populations. No transcription was found in CD34+ cells, in thymocytes, in polynuclear cells, in monocytes and in natural killer cells. Among the malignancies analyzed, HLA-G is transcribed in 2 of 13 cases of acute leukemia characterized by a monocytic contingent, in 3 of 6 CLL and in all the cases of B-NHL (n = 6). No HLA-G transcription was detected in myeloma (n = 2). The splicing type does not seem to be linked to a lymphocyte subpopulation nor to a malignant proliferation stage. These results suggest that HLA-G is a marker of mature lymphoid cells and may play an immunological function as a peptide presenting molecule. HLA-G transcription in some cases of malignancy might indicate a contribution to the tumoral progression by blocking natural killing reaction.

Publication Types:
- Corrected and republished article

PMID: 8988550

1: *Eur J Immunol* 1994 Jan;24(1):176-80

HLA-G: expression in human keratinocytes in vitro and in human skin in vivo.

Ulbrecht M, Rehberger B, Strobel I, Messer G, Kind P, Degitz K, Bieber T, Weiss EH

Institute fur Anthropologie und Humangenetik, Ludwig-Maximilians Universitat, Munchen, FRG.

Classical, polymorphic major histocompatibility complex class I molecules are expressed on most nucleated cells. They present peptides at the cell surface and, thus, enable the immune system to scan peptides for their antigenicity. The function of the other, nonclassical class I molecules in man is controversial. HLA-G which has been shown by transfection experiments to be expressed at the cell surface, is only transcribed in placental tissue and in the fetal eye. Therefore, a role of HLA-G in the control of rejection of the allogeneic fetus has been discussed. We found that HLA-G expression is induced in keratinocytes by culture in vitro. Three different alternative splicing products of HLA-G can be detected: a full length transcript, an mRNA lacking exon 3 and a transcript devoid of exon 3 and 4. Reverse transcription followed by polymerase chain reaction also revealed the presence of HLA-G mRNA in vivo in biopsies of either diseased or healthy skin.

PMID: 8020553

1: *Tissue Antigens* 1996 May;47(5):408-13

HLA-G transcription studies during the different stages of normal and malignant hematopoiesis.

Amiot L, Onno M, Renard I, Drenou B, Guillaudeux T, Le Bouteiller P, Fauchet R

Laboratoire d'Hematologie et de la biologie des cellules sanguines, Universite de Rennes I, France.

Specific expression of the non classical class I HLA-G gene on trophoblasts, the only fetal tissue in contact with maternal cells which lack MHC class I antigens, may indicate a role of this gene in fetal-maternal tolerance. We recently reported HLA-G transcription in peripheral blood leukocytes. In this work, we have investigated HLA-G transcription in hematopoietic stem cells, in different hematopoietic lineages and in malignant cells by using a RT-PCR technique. PCR amplification with primers specific to the exon 2 and the 3' untranslated region has enabled to detect HLA-G transcription in B and T cell populations. No transcription was found in CD34+ cells, in thymocytes, in polynuclear cells, in monocytes and in natural killer cells. Among the malignancies analyzed, HLA-G is transcribed in 2 of 13 cases of acute leukemia characterized by a monocytic contingent, in 3 of 6 CLL and in all the cases of B-NHL (n = 6). No HLA-G transcription was detected in myeloma (n = 2). The splicing type does not seem to be linked to a lymphocyte subpopulation nor to a malignant proliferation stage. These results suggest that HLA-G is a marker of mature lymphoid cells and may play an immunological function as a peptide presenting molecule. HLA-G transcription in some cases of malignancy might indicate a contribution to the tumoral progression by blocking natural killing reaction.

PMID: 8795141

1: *J Immunol* 1996 Jun 1;156(11):4224-31 Related Articles, Books, LinkOut

Expression of HLA-G in human mononuclear phagocytes and selective induction by IFN-gamma.

Yang Y, Chu W, Geraghty DE, Hunt JS

Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS 66160, USA.

In situ hybridization studies have shown that at early but not late stages of gestation, human placental stromal cells, many of which are macrophages (Hofbauer cells), contain HLA-G message. In this study, the HLA-G protein was identified in the macrophage-like stromal cells by immunohistochemistry using the anti-HLA-G mAb, 87G. Expression of the HLA-G gene was then analyzed in macrophage cell lines (U937, HL-60, THP-1) and blood monocytes. HLA-G mRNA identified by using reverse transcriptase PCR was consistent with production of a transcript containing intron 4, which codes for a soluble form of HLA-G. Low levels of HLA-G mRNA were identified in mononuclear phagocytes by Northern blot hybridization, and little if any HLA-G Ag was detectable. By contrast, essentially all of the cells displayed high levels of HLA-B/C H chains detected by the mAb, 4E, and B2m. Treatment of macrophage cell lines and monocytes with IFN-gamma increased steady-state levels of HLA-G mRNA, stimulated higher levels of cell surface and intracellular HLA-G Ag in a dose-dependent manner, and increased the proportions of HLA-G relative to HLA-B/C. INF-alpha and IFN-beta enhanced steady-state levels of HLA-G mRNA and in some lines modestly increased the numbers of weakly positive cells but were poor inducers of cell-surface and intracellular HLA-G and did not increase HLA-G relative to HLA-B/C. Thus, mononuclear phagocytes express low levels of HLA-G mRNA and protein, and IFN-gamma selectively enhances expression of this HLA class Ib gene relative to HLA class Ia, which could influence the repertoire of peptides presented during embryogenesis as well as during inflammatory situations in adults. Soluble HLA-G might influence both fetal and maternal immune responses.

PMID: 8666791

1: *Immunol Today* 1996 Sep;17(9):407-9 Related Articles, Books

HLA-G revisited.

Carosella ED, Dausset J, Kirszenbaum M

Dept de Recherche Medicale, Hopital St-L'ouis, Paris, France.
carosella@dsvidf.cea.fr

Publication Types:
- Review
- Review, tutorial

PMID: 8854556

Immunohistochemical analysis of malignant melanomas and nevocellular nevi with monoclonal antibodies to distinct monomorphic determinants of HLA antigens.

Ruiter DJ, Bergman W, Welvaart K, Scheffer E, van Vloten WA, Russo C, Ferrone S

Using an indirect immunoperoxidase technique, 20 nevocellular nevi, 5 dysplastic nevi, 14 primary cutaneous melanomas, and 24 metastatic melanomas were tested with a panel of monoclonal antibodies to monomorphic determinants of Class I (HLA-A,B,C) and Class II (la-like) major histocompatibility complex antigens. Class I HLA and beta 2-microglobulins were not detected on the majority of nevus cells but were expressed by 3 of 5 dysplastic nevi, by the majority of tumor cells in 12 of 14 primary cutaneous melanomas, and in 13 of 24 metastases. The different expression of Class I HLA and beta 2-microglobulins in primary and metastatic lesions suggests that loss of these antigens may be associated with progression of malignancy. Class II HLA were not detected in common nevi but were locally present in 1 of 5 dysplastic nevi, 7 of 14 cases of primary cutaneous melanoma, and all 24 cases of metastatic lesions tested. These findings suggest that increase in Class II HLA expression may be associated with progression of malignancy. The staining patterns obtained with monoclonal antibodies to distinct determinants of Class I HLA and Class II HLA were superimposable within each type of antigen. Therefore, the discrepancies in the literature about the expression of histocompatibility antigens by lesions of melanocytic origin are not likely to reflect the different specificity of the antibodies used by the various investigators.

PMID: 6204749

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1: *J Exp Med* 1997 Feb 3;185(3):385-91

Human histocompatibility leukocyte antigen (HLA)-G molecules inhibit NKAT3 expressing natural killer cells.

Munz C, Holmes N, King A, Loke YW, Colonna M, Schild H, Rammensee HG

Department of Immunology, University of Tubingen, Federal Republic of Germany.

The crucial immunological function of the classical human major histocompatibility complex (MHC) class I molecules, human histocompatibility leukocyte antigen (HLA)-A, -B, and -C, is the presentation of peptides to T cells. A secondary function is the inhibition of natural killer (NK) cells, mediated by binding of class I molecules to NK receptors. In contrast, the function of the nonclassical human MHC class I molecules, HLA-E, -F, and -G, is still a mystery. The specific expression of HLA-G in placental trophoblast suggests an important role for this molecule in the immunological interaction between mother and child. The fetus, semiallograft by its genotype, escapes maternal allorecognition by downregulation of HLA-A and HLA-B molecules at this interface. It has been suggested that the maternal NK recognition of this downregulation is balanced by the expression of HLA-G, thus preventing damage to the placenta. Here, we describe the partial inhibition of NK lysis of the MHC class I negative cell line LCL721.221 upon HLA-G transfection. We present three NK lines that are inhibited via the interaction of their NKAT3 receptor with HLA-G and with HLA-Bw4 molecules. Inhibition can be blocked by the anti-NKAT3 antibody 5.133. In conclusion, NK inhibition by HLA-G via NKAT3 may contribute to the survival of the fetal semiallograft in the mother during pregnancy.

PMID: 9053439

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Human cytomegalovirus gene products US3 and US6 down-regulate trophoblast class I MHC molecules.

J Immunol. 2000 Jan 15;164(2):805-11.

PMID: 10623826

2: Colonna M, Samaridis J, Cella M, Angman L, Allen RL, O'Callaghan CA, Dunbar R, Ogg GS, Cerundolo V, Rolink A. Related Articles

Human myelomonocytic cells express an inhibitory receptor for classical and nonclassical MHC class I molecules.

J Immunol. 1998 Apr 1;160(7):3096-100.

PMID: 9531263

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Human histocompatibility leukocyte antigen (HLA)-G molecules inhibit NKAT3 expressing natural killer cells.

J Exp Med. 1997 Feb 3;185(3):385-91.

PMID: 9053439

1: *J Biol Chem* 1994 Aug 5;269(31):20020-5 Related Articles, Books

Cooperative binding between factors RFX and X2bp to the X and X2 boxes of MHC class II promoters.

Reith W, Kobr M, Emery P, Durand B, Siegrist CA, Mach B

Jeantet Laboratory of Molecular Genetics, Department of Genetics and Microbiology, University of Geneva Medical School, Centre Medical Universitaire, Switzerland.

Transcription of major histocompatibility complex (MHC) class II genes is controlled primarily by the promoter, which contains several conserved cis-acting elements, including the X, X2, and Y boxes. We show here that RFX, the X box-binding protein that is deficient in certain MHC class II regulatory mutants, binds cooperatively with an X2 box-binding protein (X2bp) to form an RFX.X2bp.DNA complex in which the interaction of the two factors with their target sites is strongly stabilized. A functional role of this RFX.X2bp complex is consistent with mutational analysis of the X and X2 boxes of the DRA and DRB1 class II promoters. Together with previous results demonstrating cooperative binding between RFX and the Y box-binding protein NF-Y, our results indicate that RFX plays a central role in promoting cooperative binding interactions required for stable occupation of the MHC class II promoter. This may explain why the highly specific defect in binding of RFX observed in certain MHC class II regulatory mutants is associated in vivo with a bare promoter in which all of the cis-acting elements, including the X, X2, and Y boxes, are unoccupied.

PMID: 8051086

Two B cell factors bind the HLA-DRA X box region and recognize different subsets of HLA class II promoters.

Hasegawa SL, Boss JM

Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322.

The class II genes of the human Major Histocompatibility Complex (MHC) encode three isotypes of alpha/beta heterodimeric proteins, HLA-DR, -DQ, and -DP, which are responsible for presenting processed antigens to T helper lymphocytes. These MHC class II genes are expressed in a coordinate manner. The promoter regions of all MHC class II genes share a set of highly conserved elements that mediate different levels of tissue-specific and inducible transcription. One element, the X box, appears to be the major positive element in B cell-specific expression, and nuclear protein binding studies have subdivided this region into the X1 and X2 boxes. Regulatory Factor X (RFX) binds to the X1 box whereas several other factors have been described that bind to the X2 box. In this report, we further characterize the X1 binding protein RFX and show that RFX binds poorly to beta chain gene promoters. In particular, RFX does not bind to the DRB gene, which is expressed at the highest levels of all beta chain genes. In addition, we have identified an X2 box binding activity in human B cell extracts that binds with high affinity to the HLA-DRA promoter. This X2 binding protein, X2BP, binds to a different subset of class II promoters than does RFX. These findings suggest that coordinate regulation of class II expression may involve different combinations or arrangements of transcriptional elements and factors instead of a common set.

PMID: 1956787

Single base pair substitutions within the HLA-DRA gene promoter separate the functions of the X1 and X2 boxes.

Sloan JH, Hasegawa SL, Boss JM

Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322.

The class II MHC genes are expressed on the surfaces of B cells, activated T cells, and macrophages and may be induced in other cell types by IFN-gamma. The control of class II gene expression has been shown to be mediated by a series of conserved cis-acting sequences (W, X1, X2, and Y boxes) located immediately 5' to the genes. Although these sequences are conserved, the bp that are important for transcriptional regulation have yet to be identified. To address this issue with regard to the MHC gene HLA-DRA, a series of single bp substitutions spanning the conserved upstream sequences was created and analyzed for their effects on transcription in both B cells and IFN-gamma-treated fibroblasts. In addition, the effects of X1 and X2 box mutations on DNA/protein interactions were examined and compared to the transcriptional data. The results of these studies show that each of the conserved elements participate in maximal expression in B cells and that W, X1, and X2 boxes are important for IFN-gamma induction and expression in fibroblasts. Interestingly, some of the bp changes that altered B cell expression did not alter expression and IFN-gamma induction in fibroblasts, suggesting that different or altered factors control the expression of these genes in the different cell types. Mutant templates designed to eliminate the binding of X1- and X2-specific DNA binding proteins in vivo suggest that these elements and their factors may interact to promote transcription.

PMID: 1560213

X-box-binding proteins positively and negatively regulate transcription of the HLA-DRA gene through interaction with discrete upstream W and V elements.

Cogswell JP, Basta PV, Ting JP

Lineberger Cancer Research Center, University of North Carolina, Chapel Hill 27599-7295.

Previous reports have identified that the class II box, consisting of the positive regulatory X and Y boxes, is important for expression of all class II major histocompatibility genes. In this paper, we identify additional sequences upstream from the class II box that regulate constitutive transcription of a human class II gene, HLA-DRA, in the B-lymphoblastoid cell line Raji. Using 5' promoter deletions, substitution mutants, and nuclease S1 protection assays, we mapped a positive element, called W, between -135 and -117 base pairs and a negative element, called V, from -193 to -179 base pairs. Sequence comparisons revealed that W and V share homology with the HLA-DRA X box situated downstream. Gel-mobility-shift assays confirmed that the Raji nuclear proteins that bound to W and V elements were competed with by an HLA-DRA X-box oligonucleotide. These results suggest that X-box-binding proteins mediate both positive and negative effects on transcription by means of interaction with multiple elements (W, V, and X) within the same HLA-DRA gene.

PMID: 2120707

1: *J Immunol* 1997 Oct 15;159(8):3899-909 Related Articles, Books, LinkOut

Formation of a regulatory factor X/X2 box-binding protein/nuclear factor-Y multiprotein complex on the conserved regulatory regions of HLA class II genes.

Louis-Plence P, Moreno CS, Boss JM

Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322, USA.

Coordinate regulation of MHC class II genes occurs in a tissue-specific and cytokine-inducible manner. While the upstream regulatory sequences are conserved among all MHC class II genes, multiple base pair changes are found, even within the essential X box region. Analysis of all class II X boxes reveals differential binding between two transcription factors known to interact with the X box region, regulatory factor X and X2 box-binding protein (RFX and X2BP) of the HLA-DRA gene. These data presented a paradox with regard to the coordinate regulation of the class II genes if the factors though to regulate the HLA-DRA gene do not bind to the homologous sequence of all class II genes. Previous results suggested that cooperative interactions between the DNA binding proteins may be the key to understanding this paradox. Here RFX/X2BP/DNA complexes were formed on all class II isotypes regardless of the ability of the X box region to bind either factor individually. To further determine the role of the interactions between the X and Y factors, multiprotein/DNA complexes containing RFX, X2BP, NF-Y, and X-Y box DNA of the DRA and DRB genes, were formed. This quaternary complex was extremely stable to competitor DNA, with a half-life > 4 h. These results suggest that the conserved X and Y boxes of class II genes function similarly and define a single multiprotein regulatory complex for class II expression in B cells.

PMID: 9378978

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1: *Mol Cell Biol* 1990 Feb;10(2):711-9 Related Articles, Books

Mutational analysis of the DRA promoter: cis-acting sequences and trans-acting factors.

Tsang SY, Nakanishi M, Peterlin BM

Department of Medicine, Howard Hughes Medical Institute, University of California, San Francisco 94143-0724.

Class II major histocompatibility genes are expressed at high levels in B lymphocytes and are gamma interferon (IFN-gamma) inducible in many other cells. Previously, we observed that DRA promoter sequences from positions -150 to +31 determine the tissue specificity of this class II gene. Moreover, Z and X boxes located between positions -145 and -87 conferred B-cell specificity and IFN-gamma inducibility upon a heterologous promoter. In this study, sequences from positions -145 to -35 in the DRA promoter were systematically mutated by using oligonucleotide cassettes. Z (-131 to -125), pyrimidine (-116 to -109), X (-108 to -95), Y (-73 to -61), and octamer (-52 to -45) boxes were required for B-cell specificity and, with the exception of the octamer box, for IFN-gamma inducibility. Z box and sequences flanking Z and X boxes helped to determine low levels of expression in T and uninduced cells. In phenotypically distinct cells, shared and distinct proteins bound to these conserved upstream sequences. However, few correlations between expression and DNA-binding proteins could be made. Similar proteins bound to Z and X boxes, and the Z box most likely represents a duplication of the X box.

PMID: 2105459

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